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Exploring TNFR1: from discovery to targeted therapy development

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Abstract

This review seeks to elucidate the therapeutic potential of tumor necrosis factor receptor 1 (TNFR1) and enhance our comprehension of its role in disease mechanisms. As a critical cell-surface receptor, TNFR1 regulates key signaling pathways, such as nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK), which are associated with pro-inflammatory responses and cell death. The intricate regulatory mechanisms of TNFR1 signaling and its involvement in various diseases, including inflammatory disorders, infectious diseases, cancer, and metabolic syndromes, have attracted increasing scholarly attention. Given the potential risks associated with targeting tumor necrosis factor-alpha (TNF-α), selective inhibition of the TNFR1 signaling pathway has been proposed as a promising strategy to reduce side effects and enhance therapeutic efficacy. This review emphasizes the emerging field of targeted therapies aimed at selectively modulating TNFR1 activity, identifying promising therapeutic strategies that exploit TNFR1 as a drug target through an evaluation of current clinical trials and preclinical studies. In conclusion, this study contributes novel insights into the biological functions of TNFR1 and presents potential therapeutic strategies for clinical application, thereby having substantial scientific and clinical significance.

Keywords TNFR1, TNF, Therapy, Inflammation, Apoptosis

Introduction

Tumor necrosis factor receptor 1 (TNFR1) is a protein located on the surface of cells that primarily transmits signals by interacting with tumor necrosis factor-α (TNF-α) and participates in biological processes such as inflammation, cell survival, and apoptosis. This receptor is part of the tumor necrosis factor receptor (TNFR) superfamily and plays a crucial role in mediating the effects of TNF-α, a cytokine involved in systemic inflammation [1]. TNFR1 has several important features in its molecular structure. It usually exists in a trimeric form, which is the basis for TNF-α binding. TNFR1's external structure has multiple binding sites, allowing it to bind to TNF-α. Specifically, TNFR1's binding sites interact with the structure of TNF-α, allowing TNF-α to bind to TNFR1 through its three identical binding sites [2, 3].

TNF-α exists in two forms: membrane-bound TNF (tmTNF) and soluble TNF (solTNF). The distinction between these two forms is crucial as they play different roles in various physiological and pathological processes. tmTNF primarily signals through tumor necrosis factor receptor 2 (TNFR2), mediating protective and reparative effects, while solTNF, which mainly signals through TNFR1, promotes pro-inflammatory and detrimental functions [4–6]. The intricate mechanisms by which

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TNFR1 influences cellular responses, including survival, apoptosis, and inflammation, have been the focus of extensive research. The regulation of TNFR1 signaling is highly complex, involving both endogenous and exogenous factors. Upon binding with TNF-α, TNFR1 activates various intracellular signaling pathways, which is essential for regulating immune responses and cell survival [7]. Moreover, TNFR1 is implicated in the modulation of cellular functions that can lead to both protective and detrimental outcomes. For instance, while TNFR1 signaling can promote cell survival and proliferation, it can also trigger apoptotic pathways under certain conditions, contributing to tissue injury and inflammation [8]. The complexity of TNFR1 signaling is further highlighted by its interactions with other proteins, such as SRC associated in mitosis of 68 Kd (Sam68), which is necessary for the proper activation of TNF-α signaling [9]. Recent studies have highlighted the dual role of TNFR1 in promoting both cell survival and apoptosis, depending on the context and the presence of other signaling molecules [10]. For instance, TNFR1 can activate pro-survival pathways through the recruitment of various adaptor proteins, while simultaneously triggering apoptotic pathways under certain conditions [11]. This complexity is further underscored by the involvement of post-translational modifications, such as ubiquitination, which modulate TNFR1 signaling outcomes [12].

TNFR1 signaling in various diseases is receiving increasing attention. TNFR1-mediated signaling pathways are crucial in the pathogenesis of diseases such as autoimmune disorders, chronic inflammatory diseases, and cancer. Currently, several anti-TNF-α therapies are available for diseases such as rheumatoid arthritis (RA) and Crohn's disease, which alleviate inflammation by inhibiting TNF-α activity [13]. However, the clinical application of this approach has yielded mixed results, with some studies reporting limited efficacy [14, 15] and others suggesting potential harm, such as increased mortality [16]. The therapeutic potential of targeting TNFR1 signaling is also being explored, particularly in the treatment of inflammatory diseases and cancers. Selective inhibition of TNFR1 has been proposed as a strategy to mitigate the adverse effects associated with broader TNF signaling blockade, thereby enhancing therapeutic efficacy while reducing side effects [17]. In such, this study aims to review TNFR1's discovery, structural characteristics of its ligands and receptors, its expression in cells, the TNFR1-mediated signaling pathway and its significance, as well as its role in various diseases and targeted therapies, and to explore the delicate balance of TNFR1 in health and disease, providing a theoretical basis and practical implications for the development of more effective therapeutic regimens.

Structure and expression of TNFR1

Although TNFR1 (TNFRSF1a, CD120, p55) was first reported in 1985, the exploration of the TNF system indeed originated in the 19th century. In 1893, the tumor regression after the bacterial infection in cancer patient was documented by Coley [18]. However, bacteria clearly do not have the ability to kill tumor cells, as the study grows by leaps and bounds, it was realized that a host-derived factor which initiate the "hemorrhagic necrosis" of tumors and named TNF in 1975, was induced by exogenous stimulation, like endotoxin [19, 20]. Bluter et al. identified TNF-α from macrophages in 1985, while Frederick et al. characterized the high-affinity TNFR1 receptor during cytotoxicity studies [21]. The shared receptors TNFR1 and TNFR2 were found to mediate similar functions for lymphotoxin (LT, TNF-β) and TNF-α, including apoptosis, necrosis, inflammation, and cancer progression [22]. However, the physiological relevance of TNFR1 and TNFR2 was unclear until the establishment of the TNFR1 knockout mice in 1994 which identified that the TNFR1 actually monopolizes the TNF-meditated signaling in inflammation [23]. Nowadays, TNFR1 is recognized as a central receptor in the immune system, with roles in bacterial defense, inflammation, and immune modulation.

Structure of TNFR1

The full-length 55KD type I transmembrane protein TNFR1 is composed of three parts, including extracellular, transmembrane, and intracellular, which contains various domains essential for ligand-mediated signal transduction [24–26]. There are four cysteine-rich domains (CRD1, CRD2, CRD3, and CRD4) characterized by six cysteine repeat motifs, which is the conserved protein module of TNFRSF member, in the extracellular region (28KD) comprised of 182 amino residues (Leu^{1}-Thr^{182}) [25, 27] (Fig. 1). Among them, the aa^{56}-aa^{73} of CRD2 and aa^{107}-aa^{114} are identified as the crucial binding sites in the interaction surface between TNFR1 and its ligands [27]. In addition to intermolecular force in interaction surface, the ligand-TNFR1 interaction also depended on the trimerization of TNFR1. Interestingly, the initiation of trimeric TNFR1 precedes binding by TNF-α, reflected by that in its resting state, TNFR1 is more prone to clustering. This suggests that the formation of trimeric TNFR1 is not solely driven by TNF-α [28]. It has been identified that α-helix dominant topology (Transmembrane helix, TMH) formed by 22 amino acids in TMR, and the pre–ligand-binding assembly domain (PLAD) located within extracellular region (ECR) (aa^{1}-aa^{54}), serve as the primary driving forces behind TNFR1 trimerization [26, 29, 30].

Unlike the ECR and TMH responsible for self-oligomerization and ligand binding, the domains located

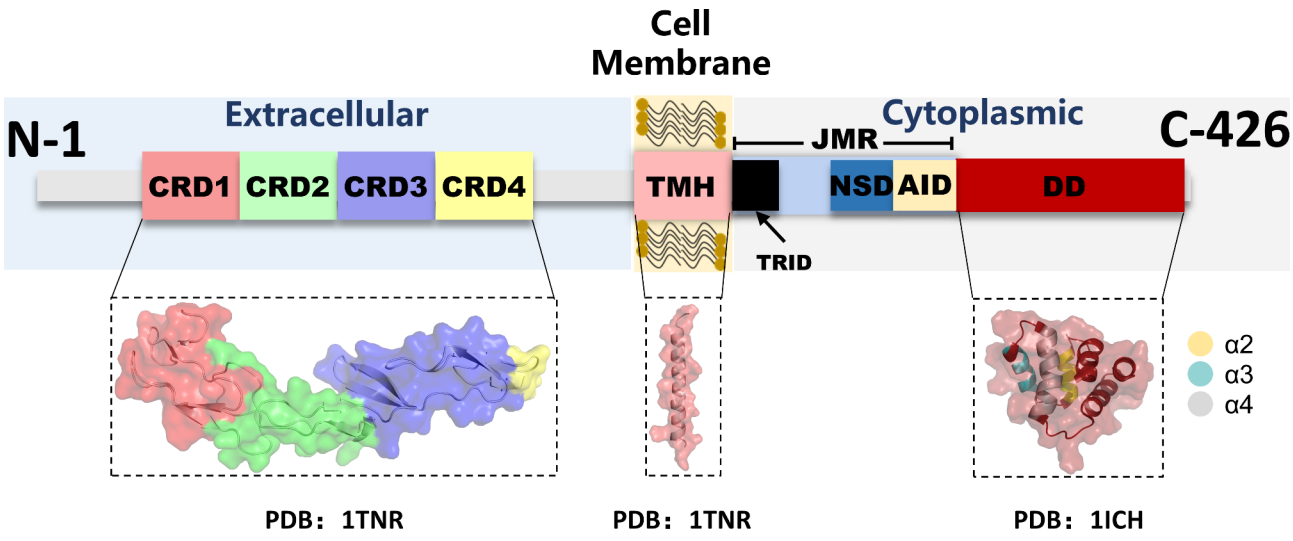

Fig. 1 The structural characteristics of human TNFR1

within the cytoplasmic region (CR) play a more crucial role in transmitting inward signals. The death domain (DD) located in the C-terminal of TNFR1 within ECR serve as a prerequisite for TNFR1 responded to TNF by recruiting adaptor proteins such as TNFR1-associated death domain protein (TRADD) [31]. Furthermore, TRADD recruits additional signaling molecules, including TNFR-associated factor 2 (TRAF2), receptor-interacting protein kinase (RIPK), and Fas-associated protein with a novel death domain (FADD), to assemble the Death Inducing Signaling Complex (DISC), which triggers apoptosis and programmed necrosis or forms a pro-inflammatory membrane signaling complex [32]. DD is structurally composed of six trans-parallel α-helices, with key amino acid residues W342 to L349 (α-2), D353 to L361 (α3), and L367 to R380 (α4) playing pivotal roles in DD-TRADD interaction or DD oligomerization [33].

Adjacent to the cell membrane, a specific amino acid sequence known as the neutral sphingomyelinase domain (NSD) in the juxtamembrane region (JMR) has been identified as an inducer of cell death [34, 35]. It is noteworthy that NSD-mediated cell death occurs independently of the DD [36]. By up-regulating intracellular ceramide content, NSD can cause mitochondrial dysfunction and ultimately lead to cellular demise [37, 38]. Following the TMH, a TNFR1 internalization domain (TRID) consisted by 9 aminos located at JMR is identified, which facilitates TNFR1 internalization and is considered to be the primary reason for its diverse biofunctions [39]. This is due to the shedding of intracellular segments from the membrane, which recruit various signal transduction-related molecules and subsequently elicit diverse cellular event. Additionally, the AIP-binding domain (AID) located at the termini of JMR also plays a pivotal role in the assembly of TNFR1 signaling complex [40]. Upon stimulation by TNF-α, AID-bound AIP dissociates from resting TNFR1 and directly participates in recruiting apoptosis signal regulating kinase-1. In addition to its promoting cell death activity, JMR also harbors the binding site for TNFR1 associated binding protein 2 (TRAP2), brain and reproductive organ-expressed protein (BRE) and hosphatidylinositol-4-phosphate 5-kinase (RIP5K), which locates between TRID and NSD, crucial for transducing pro-cell death and proinflammatory signals by TNFR1 [41–43]. In general, the diverse domains enable TNFR1 to conduct different or even opposite biological signals through a variety of mechanisms, including pro-inflammation, pro-survival, pro-apoptosis, and pro-necrosis which will be described in more detail below.

Expression of TNFR1

Currently, TNFR1 expression is across cell lineages that lack cell selectivity, which may be associated with the immune activity of the organism. Promoting the cell necroptosis, cytokines expression and the immune cell activation, and the repaid response for exogenous infection, lead the TNFR1 an important receptor in innate immune. While the innate immune system's non-specificity and high sensitivity necessitate broad expression of TNFR1 throughout the organism. Based on the gene-expression levels of 27 different tissue samples obtained from the 95 human individuals, TNFR1 is found to be ubiquitously expressed in most tissues, as suggested by Linn Fagerberg [44]. This indicates that TNFR1 exhibiting the constitutive expression akin housekeeping gene, which is further supported by the gene sequence of TNFR1.

Nucleotide sequences of TNFR1-gene (TNFRSF1A in human and tnfrsf1a in mouse) span 12 kb, consisting of

10 exons and 9 introns, located on the first subband of the third subband of human chromosome 12 region 1 (12p13.31). However, the promoter sequence located in 5' flanking region plays a pivotal role in ensuring constitutive expression of TNFR1-gene. Except a crucial promoter sequence TATA box which is responsible for binding to RNA polymerase and two GC-enrich elements that exhibited enhancer feature in many eukaryotic genes [45], there are numerous transcription regulation sequence for binding function protein in 5' flanking region of tnfrsf1a, as following [46].

Two sequences resembling Cytokine-1motify (CK-1) were identified within the promoter region of tnfrsf1a (-218 to -209 and 74 to 83), which have been proposed as TNF-responsive elements (TNFREs) and contribute to the constitutive activity of TNFR1 through binding with a constitutively expressed nuclear factor, p50 homodimer of nuclear factor kappa-B (NF-κB) induced by TNF-α [47, 48]. Additionally, the CCAAT/enhancer binding protein (C/EBP) responsive element consensus sequence, located at + 5 to + 12, serves as another means for regulating the TNFR1's constitutive activity. The C/EBP transcription factor is involved in various cellular processes such as energy metabolism, proliferation and differentiation, and inflammation [49, 50]. It has been identified that tumor necrosis factor response element (TNFRE) is also located within the gene coding regions of interleukin-2 (IL-2), IL-3, Glucocorticoid-stimulating factor, and Glucocorticoid macrophage-stimulating factor [51]. Additionally, C/EBPRE exists in the promoters of IL-6, IL-4, IL-5, and TNF-α.

Although TNFR1 is expressed constitutively in various cells, its expression isn't static but rather dynamic and regulated by other regulatory genes located in 5'flanking region. The regulatory elements identified include three homology sequences responsive to NF-κB located at -924 to -915, -862 to -853, and – 504 to -495, respectively. Additionally, there is one consensus sequence responsive to IL-6 located at -679 to -674. The NF-κB and IL-6 responsive elements bind to nuclear factor NF-κB and signal transducer and activator of transcription (STAT), respectively, thereby inducing the transcription of the TNFR1 gene through their involvement in inflammation. Furthermore, the expression of TNFR1 is upregulated, which may be initiated by other cellular events such as proliferation, differentiation, and cellular homeostasis [52, 53]. This is supported by the identification of five binding sites for activator protein 1 transcription factors and two binding sites for activator protein 2 in the 5' flanking region [53–55]. Certainly, in addition to the aforementioned positive regulatory elements, there are also negative regulatory elements present within the TNFR1-gene promoter that located at the gene sequence between – 832 to -508. Deletion of these elements results in upregulation of TNFR1 expression. Taken together, TNFR1 constitutive expression in various tissues is dependent on the promoter within its gene code, which contains complicated regulatory elements that enable rapid response to organic immunization activities. This feature favors the activation of immune cascades.

Mechanisms and outcomes of TNFR1 signaling

TNFR1, a key TNF receptor, plays a pivotal role in immune responses. Initially recognized for initiating cell-death signaling, TNFR1's functions extend to pro-survival and pro-inflammatory pathways as research advances. The receptor's activation is modulated by cytoplasmic protein complexes: complex I promoting inflammation and complex II inducing cell death. TNFR1-induced lytic death releases cellular debris, potentiating immune responses. Death induction occurs via caspase-8 activation in complex II, triggered when complex I's membrane proximal domain is disrupted, representing a self-protective mechanism to maintain immune homeostasis.

Pro-inflammatory

The intracellular complex I, centered around TNFR1 DD, rapidly assembles and activates inflammatory genes, after trimeric TNF binds to TNFR1's CRDs on the cell membrane (Fig. 2). The first recruited protein, TRADD, harbors a C-terminal DD domain that engages in a tight heterodimeric with the N-terminal of TNFR1 through strong polarity of DD [56, 57]. Subsequently, receptor-interacting protein kinase 1 (RIPK1) and TNFR-associated factor 2/5 (TRAF2/5) are recruited by TRADD and anchored to its C-terminal DD and N-terminal domain (TRADD-N), respectively [58]. TRAF2/5 acts as a versatile scaffold protein, linking the N-TRAF region within its C-terminal TRAF domain to the Baculoviral IAP Repeat (BIR) domain of cellular inhibitor of apoptosis protein 1/2 (cIAP1/2), thereby facilitating the assembly of an E3 ubiquitin ligase complex [59–63]. Notably, despite possessing five Zinc finger motifs, TRAF2 lacks intrinsic E3 ubiquitin ligase activity and serves exclusively as an adaptor protein [64, 65]. Upon formation of the E3 ubiquitin ligase complex, RIPK1 undergoes rapid modification with a K63-linked polyubiquitinated chain at lysine residue 367. This modification creates a platform for the recruitment of Transforming Growth Factor-β Activated Kinase 1/TGF-β Activated Kinase 1 Binding Protein 1 (TAB/TAK) and IκB Kinase (IKK) (including IKKα/IKKβ/ NF-κB Essential Modulator (NEMO)) following E3 ubiquitin ligase complex formation [66]. cIAP1/2 can undergo self-ubiquitination using K63-linked polyubiquitin chains, promoting interactions with Heme-oxidized IRP2 Ubiquitin Ligase-1 (HOIL-1 L) and HOIL-1-interacting protein (HOIP), thereby facilitating the recruitment of the linear ubiquitin chain assembly complex

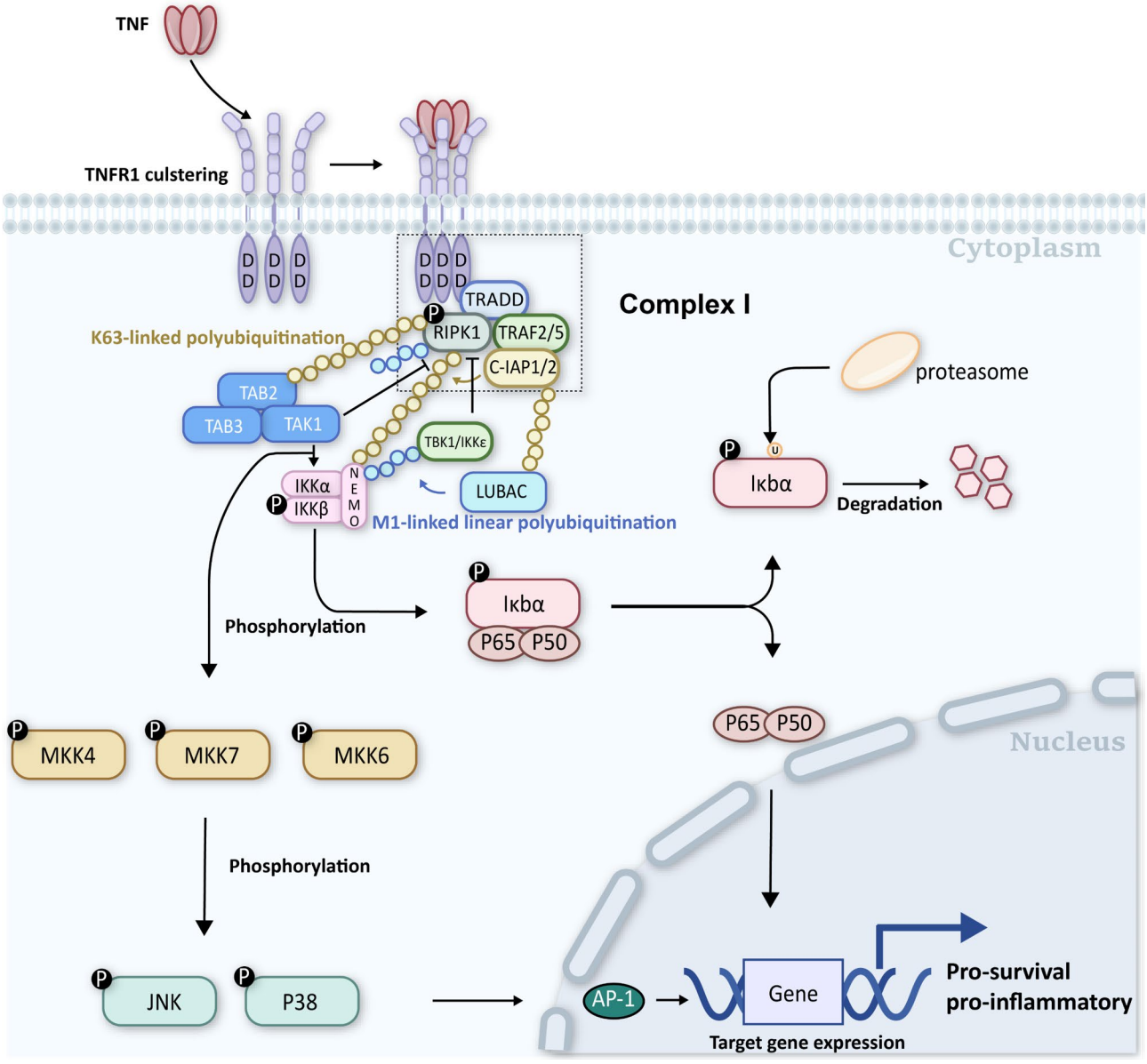

Fig. 2 Component, activation and regulation of the intracellular complex I

(LUBAC). LUBAC is composed of SHANK-associated RH domain-interacting protein (SHARPIN), HOIL-1 and HOIP, which mediate the synthesis of linear ubiquitin chains [67]. Its interaction with cIAP1 results in a denser ubiquitination network for complex I, thereby enhancing the functional interdependence among proteins. The linear ubiquitination of Met1 (M1) by LUBAC enhances the binding affinity of NEMO to K63-linked ubiquitin chains, thereby augmenting its interaction with RIPK1 and prolonging its retention at the adaptor platform. Furthermore, LUBAC plays a crucial role in the recruitment and phosphorylation of RIPK1 by TANK-binding kinase 1 (TBK1) and IKKε, which may inhibit RIPK1 kinase-dependent cell death and facilitate the formation of complex I [68].

Furthermore, LUBAC modifies RIPK1 with M1-linker (linear) ubiquitin chains to enhance the recruitment of TAB/TAK and IKK complex, which is supported by the observation from Tang Yong's group that the Ripk1K376R/K376R cell death event occurs upon the stimulation with TAK1 or IKK inhibitor [66, 67, 69–72]. TAK1 and IKKα/IKKβ, once recruited, phosphorylate RIPK1, stabilizing complex I by reducing its pro-death function and enhancing protein recruitment. Additionally, the activation of these kinases is vital for the downstream signaling pathways of NF-κB and MAPKs. The spatial proximity of TAK1 and IKKβ on the ubiquitination platform

enables TAK1-mediated phosphorylation of IKKβ at serine residues S177 and S181, leading to the activation of IKKβ. This activation results in the phosphorylation and subsequent degradation of IκB, permitting the nuclear translocation of the transcriptionally active NF-κB complex (comprising p65 and p50) to initiate gene expression [73–76]. Lastly, as a member of MAPK kinase kinase (MAPKKK) family, TAK1 also can activate the transcription factor activator protein-1 (AP-1) to promote the expression of target gene through the cascade phosphorylation of Mitogen-Activated Protein Kinase Kinases-c (MKKs)-P38/ Jun N-terminal kinases (JNK) [77].

In summary, upon stimulation by TNF-α, the DD of TNFR1 recruits the adaptor protein TRADD, facilitating the formation of complex I with scaffold proteins such as RIPK1, cIAP1, LUBAC, and NEMO. This complex subsequently activates TAK1 and IKK, which in turn activate NF-κB and MAPKs, leading to the expression of pro-inflammatory and pro-survival genes.

Pro-cell death

The transduction of TNFR1-mediated cell death signal is reliant on the formation of complex II, which is derived from complex I in a continuous and interdependent manner. RIPK1 and TRADD are crucial element in this transition, although the transduction of cell death signals is a multifaceted process [78]. The assembly of complex I upon TNFR1 activation is contingent upon the interaction of multiple proteins, including death-checkpoint inhibitors that prevent the formation of complex II. The assembly of complex II is initiated by the inactivation of death checkpoints or other pathway interferences, thereby activating cell death pathways such as apoptosis, necroptosis, or pyroptosis. The precise mechanisms underlying the activation of TNFR1-mediated cell death signals remain incompletely understood. Various checkpoints regulate the modifications of RIPK1 and TRADD, determining the specific form of complex II, which may be IIa, IIb, or the necrosome (IIC).

Apoptosis

The compact ubiquitination network is essential for protein interactions and stabilizing complex I. In complex I, RIPK1 is ubiquitinated by E3 ligases like cIAP1/2 and LUBAC, which enhances its scaffold function and complex I stability. Meanwhile, RIPK1's kinase activity is inhibited by phosphorylation by ubiquitin network members such as IKK and TAK [79]. Thus, the balance of RIPK1 phosphorylation and ubiquitination is critical for regulating cell death and survival signals (Fig. 3).

When ubiquitination is compromised, such as through the degradation of c-IAP by Smac, stimulation by TNF results in the translocation of RIPK1 from complex I to the cytosol, where it undergoes de-ubiquitination by CYLD [80]. Subsequently, RIPK1 associates with FADD and caspase-8 to form complex IIb via its DD, facilitating the activation of caspase-8 through FADD-mediated cleavage. As apoptosis becomes fully activated, caspase-8 inhibits necrosis by cleaving RIPK3 and initiates a cascade of apoptotic signals to effector caspases through a heterologous activation mechanism.

Notably, TNF-induced NF-κB activation occurs independently of RIPK1-dependent apoptosis, suggesting that TRADD can activate NF-κB following the dissociation of RIPK1 from complex I. This observation appears to contradict the typical RIPK1 apoptosis pathway, which generally involves the suppression of NF-κB-targeted genes such as cellular Fas-associated death domain-like interleukin-1β-converting enzyme inhibitory protein (c-FLIP) and cIAP1/2 promote the translocation of RIPK1 and caspase-8 to the cytosol [81]. Research indicates that the overexpression of TRADD inhibits RIPK1-dependent apoptosis and that TRADD is absent from complex IIb. This regulation supports a controlled apoptotic process, enabling the cell to modulate NF-κB signaling, balance RIPK1-dependent death signals, and prevent pathological apoptosis, thereby maintaining cellular homeostasis [82, 83] (Fig. 3).

Increasing evidence suggests that multiple checkpoints, beyond cIAP1/2 and c-FLIP, participate in the RIPK1-dependent signaling pathway. Apoptosis mediated by TNFR1 can also proceed via a pathway independent of NF-κB signaling, specifically through the formation of RIPK1-independent Complex IIa. In this pathway, TRADD recruits and activates FADD, circumventing RIPK1. Various factors, such as TNFR2 signaling, may affect TRADD's preference for recruiting FADD over RIPK1, potentially by competing for TRAF2/5 binding sites, thereby facilitating TRADD-FADD interaction. Following recruitment, the TNFR1 terminal death domain, along with TRADD, undergoes internalization [82]. Consequently, the membrane-bound TRADD decreasing and FADD's NF-κB inhibitory activity may contribute to Complex IIa's inability to activate NF-κB signaling, although as the NF-κB signaling pathway is attenuated, the intracellular levels of c-FLIP and cIAP1/2 are likely to decrease, potentially leading to further activation of complex IIb. Similar to the ability of TRADD to rescue RIPK1-mediated apoptosis, RIPK1 in embryonic cells also successfully inhibited TRADD-induced cell death. In summary, RIPK1 and TRADD negatively regulate each other in their apoptosis-inducing functions, and it is tempting to speculate that the balance between the two under normal physiological conditions may be one of the reasons why TNFR1 preferentially transmits pro-inflammatory and survival signals. Similar to TRADD's ability to rescue RIPK1-mediated apoptosis, RIPK1 also

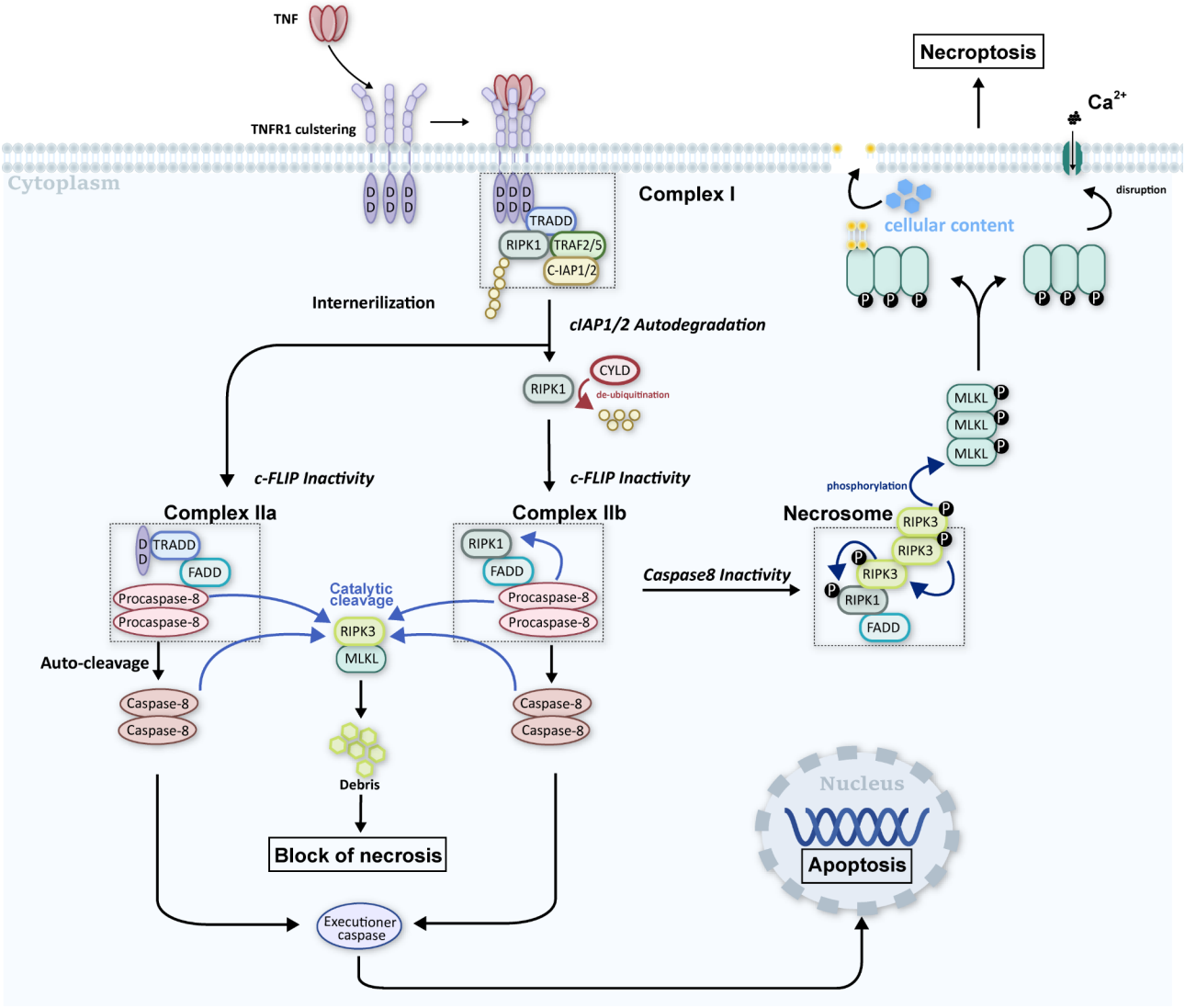

Fig. 3 Apoptosis and necroptosis signaling pathways associated with TNFR1

effectively inhibits TRADD-induced cell death in embryonic cells.

In summary, RIPK1 and TRADD mutually negatively regulate each other in their apoptosis-inducing functions, and it is tempting to speculate that the balance between the two under normal physiological conditions may be one of the reasons why TNFR1 preferentially transmits proinflammatory and survival signals.

Necroptosis

Necroptosis, a form of programmed necrosis, is triggered by RIPK1 activation in response to TNF [84]. This pathway, which combines features of necrosis and apoptosis, is regulated by phosphorylation and ubiquitination. It leads to cell membrane rupture, content leakage, and inflammation. The process involves RIPK1 detaching from the annexin complex due to TNF signaling, followed by the formation of complex IIb with FADD and caspase-8 (Fig. 3).

In this process, the interaction between RIPK1 and FADD is not only reliant on their death domains but also subject to regulation by the kinase activity of RIPK1, which is linked to the phosphorylation status of receptor-interacting protein kinase 3 (RIPK3) [85]. However, given that the phosphorylation of RIPK1 by RIPK3 is feeble, it may be necessary for other factors to participate in activating the kinase activity of RIPK1. Caspase-8, a pivotal regulator of RIPK3 phosphorylation, engages with RIPK1 via the RIP homotypic interaction motif (RHIM) domain. In the absence of active caspase-8, RIPK3 and RIPK1 interact, resulting in enhanced phosphorylation and kinase activity of RIPK1, which facilitates the stabilization of FADD binding to form the Necrosome.

Consequently, caspase-8 serves as a critical checkpoint within the necroptotic pathway.

Within necrosomes, RIPK3 augments its kinase activity through the formation of homodimers or multimers and subsequent auto-phosphorylation, thereby contributing to the activation of the mixed lineage kinase domain-like (MLKL) protein [86]. Furthermore, the exposing of N-terminal 4-helical bundle domain oligomerization of MLKL [87] is facilitated by RIPK3-mediated phosphorylation at Thr357 and Ser358, which leads to the oligomerization of MLKL and translocation to the cell membrane [88–90]. At the membrane, MLKL disrupts the lipid bilayers, resulting in the leakage of cellular contents [91, 92]. Additionally, MLKL can interact with membrane proteins such as transient receptor potential melastatin-related 7 (TRPM7), perturbing calcium and sodium ion homeostasis and ultimately causing cell membrane rupture.

Compared to pro-apoptotic signaling, RIPK1-initiated necroptosis can further amplify the inflammatory signal and promote an inflammatory cascade effect through intracellular substance leakage [93]. Therefore, it can be inferred that TNF-dependent necroptosis is highly susceptible to virus infection in vitro, as evidenced by the extensive formation of the RIPK1-RIPK3 complex following vaccinia virus infection. In summary, RIPK3 regulates necroptosis by initiating a pro-necrotizing kinase cascade, which has significant implications against innate inflammatory responses to viral infections.

Pyroptosis

The in vivo role of TNFR1 extends beyond the signal transduction mediated by complex I and complex II, encompassing several mechanisms that remain incompletely understood. In recent years, a novel downstream signaling complex of TNFR1, namely TRIF-dependent complex, has been discovered [94, 95]. Unlike complexes I and II, it is not ubiquitous but specifically exists in hematopoietic stem cell subsets, providing an important mechanism for TNF to regulate immune cells.

CD14 is a cell-specific protein predominantly expressed in neutrophils and macrophages, among others, that facilitates the endocytosis of TNFR1 and promotes the formation of intracellular vesicles [96] (Fig. 4). During this process, the DD located at the C-terminus of TNFR1 retains its ability to recruit RIPK1 and localize TRIFosome to CD14-rich regions via TRAM, thereby facilitating the interaction between TRIF and RIPK1. The interaction between RIPK1 and TRIF enhances the protein recruitment capacity of RIPK1, facilitating its ability to recruit TRAF3, TBK1, and NEMO to form a pro-inflammatory signaling complex known as the TRIF-dependent pro-inflammatory TRIFosome. Notably, the formation of TRIF-associated signaling complexes

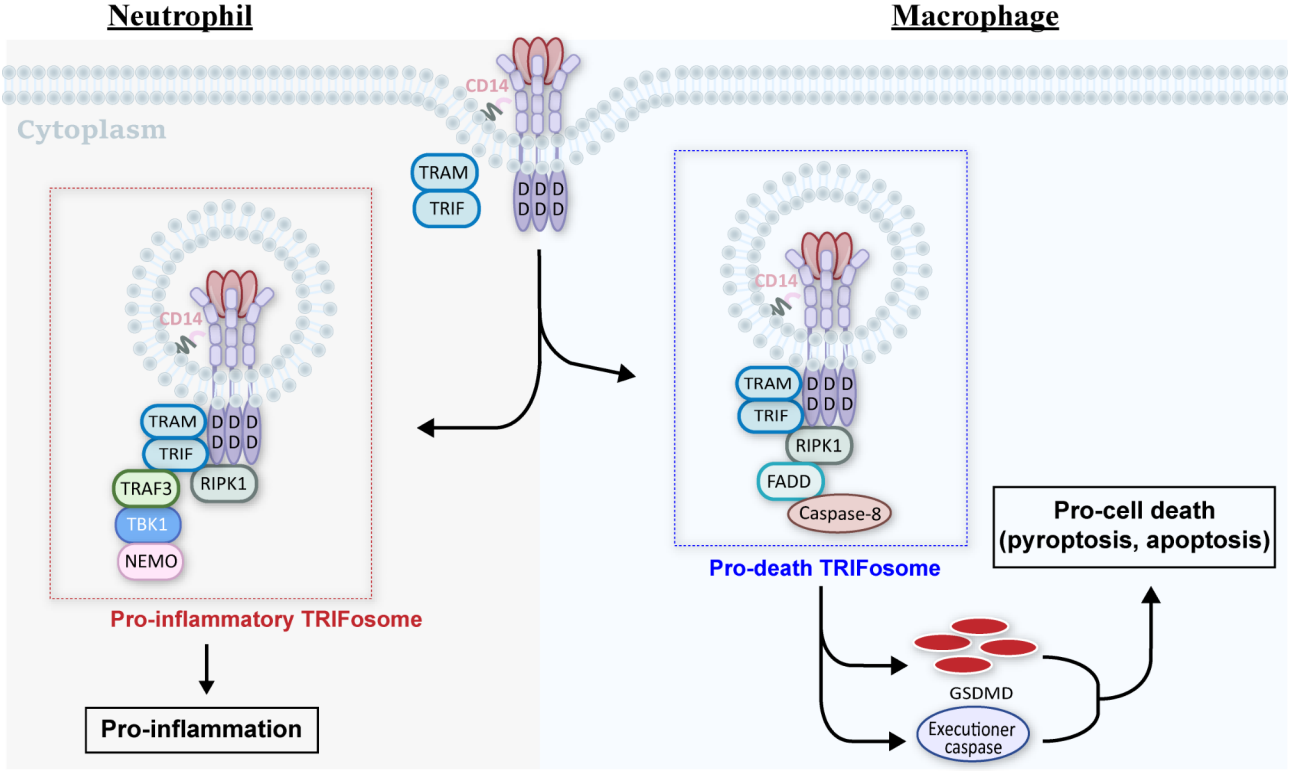

Fig. 4 CD14 expression in immune cells and function associated with TNFR1

is under the regulation of TAK1 activity. Inhibition of TAK1 leads to an enhancement in RIPK1's ability to recruit FADD, which subsequently recruits caspase-8 to form the pro-death TRIFosome complex. This complex promotes apoptosis by activating gasdermin D (GSDMD) and other executive caspases, leading to pyroptosis [97].

TNFR1 signaling in health and disease

TNFR1 plays a crucial role in the occurrence and progression of various diseases, particularly in conditions such as inflammation, cancer, metabolic disorders, etc. (Fig. 5). Abnormal activation or dysregulation of TNFR1 expression may lead to the following diseases:

Inflammatory diseases

This study introduced the role of TNFR1 in typical inflammation-related diseases:

The pathogenesis of autoimmune diseases is usually closely related to the abnormal activation of TNF-α and its receptors. Research shows that TNFR1 plays a critical role in the development of many autoimmune diseases. Excessive activation of TNFR1 may lead to chronic inflammation and promote the maintenance of autoimmune responses [98]. It is a pathological condition involving multiple organs and systems, characterized by chronic inflammation, tissue damage, and functional impairment [99]. For example, rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation, in which TNF-α plays a central role in its pathogenesis. Excessive activation of TNFR1 can lead to the

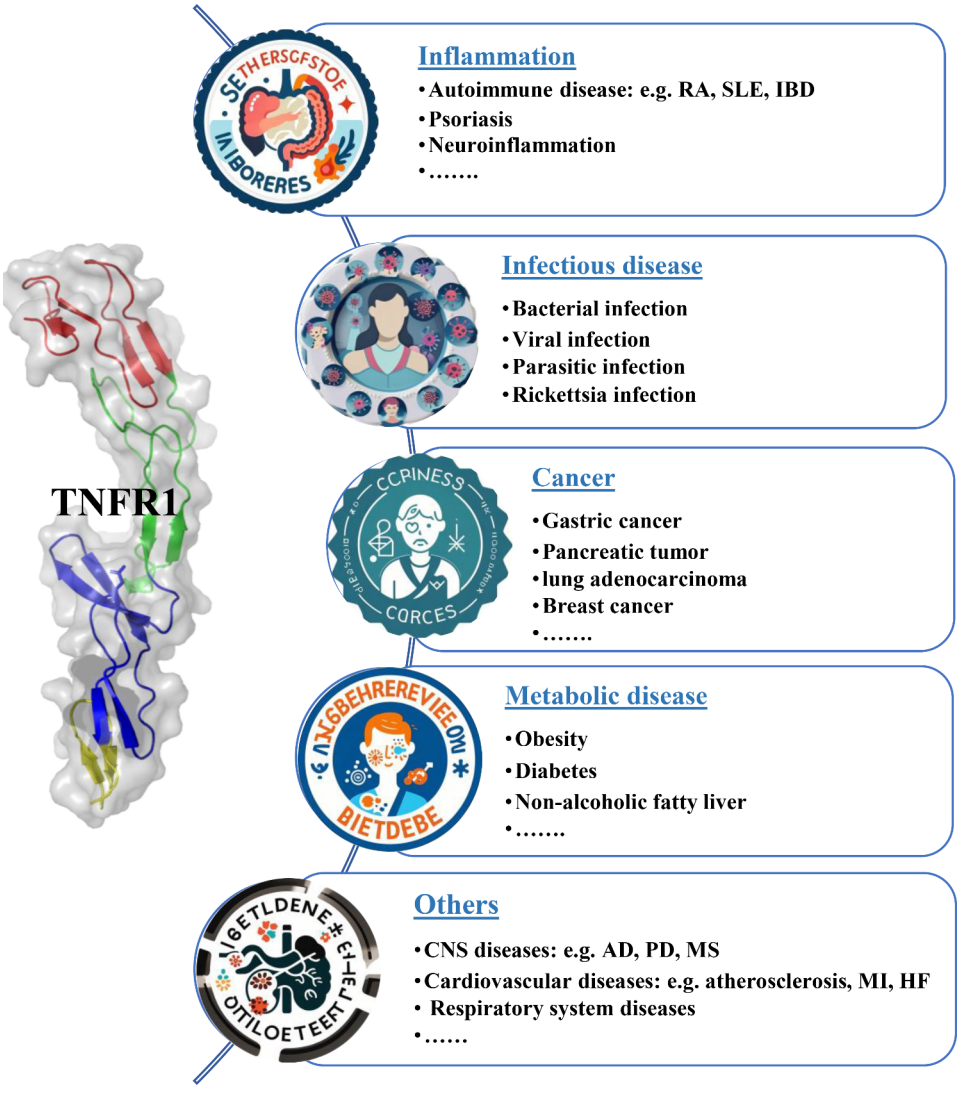

Fig. 5 TNFR1 associated with different diseases. RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; IBD: inflammatory bowel disease; CNS: central nervous system; AD: Alzheimer's disease; PD: Parkinson's disease; MS: multiple sclerosis; MI: Myocardial infarction; HF: Heart failure. "....." indicates that there are other diseases not listed

release of inflammatory factors in the joint, aggravating the condition. The dysregulation of these immune responses, coupled with the presence of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), leads to a chronic inflammatory state that characterizes RA [100]. The use of TNF-α inhibitors has significantly improved the clinical outcomes of RA patients, but there are also cases of treatment failure, which suggests that targeting TNFR1 and its downstream signaling pathways presents a promising therapeutic strategy to mitigate inflammation and prevent joint damage in RA patients [101, 102]. In inflammatory bowel disease (IBD), elevated levels of TNF-α and its receptors have been observed, correlating with disease severity and the extent of mucosal damage [103]. Activation of TNFR1 may cause damage to intestinal epithelial cells and exacerbate inflammation, affecting the intestinal barrier function and leading to worsening of the condition [99]. Moreover, TNFR1 signaling has been implicated in the pathogenesis of systemic lupus erythematosus (SLE), where lupus serum immunoglobulin G (IgG) induces skin inflammation through TNFR1-mediated pathways [104].

The TNF-α/TNFR1 axis is crucial in mediating the inflammatory processes that lead to the characteristic skin lesions of psoriasis. This signaling pathway activates various downstream inflammatory responses that contribute to keratinocyte hyperproliferation and immune cell infiltration in the skin, which are central to the development of psoriatic plaques [17]. Moreover, the dysregulation of TNF-α signaling can lead to paradoxical effects, such as the exacerbation of psoriasis in patients treated with anti-TNF therapies [105]. This highlights the complexity of the TNF-α/TNFR1 axis in psoriasis, where both excessive activation and inhibition of this pathway can influence disease severity and treatment outcomes [106].

In addition, the activation of TNFR1 in spinal cord tissue is closely related to the occurrence of neuroinflammation and related clinical symptoms [107]. Specifically, TNFR1 promotes pro-inflammatory responses in spinal cord and brain tissue during neuroinflammation, which may lead to neuronal damage and dysfunction, thereby aggravating clinical symptoms [107]. TNFR1 not only directly affects neurons, but also regulates neuroinflammation through interactions with glial and immune cells. Activation of glial cells releases more pro-inflammatory cytokines, further exacerbating the inflammatory response [108]. In some cases, TNFR1 antagonist therapy may lead to increased inflammation, suggesting that TNFR1's role in regulating inflammation is not unidirectional [109].

Infectious disease

TNFR1's interaction with pathogens not only affects the host's response to infection but also determines the severity and outcome of the disease. As the first line of defense against bacterial, viral, and other pathogenic infections, TNFR1 is involved in regulating the host's immune response. Studies have shown that TNFR1 enhances the host's resistance to infection by promoting inflammatory responses and the expansion of effector T cells [110, 111]. In models of infectious diseases in animals lacking TNFR1, animals show better resistance, suggesting that TNFR1 may promote the survival or spread of pathogens in some case [111, 112].

For bacterial infections, TNFR1 promotes the recruitment of neutrophils in the skin, which is crucial for the control of local infections. Neutrophils are the main immune cells that defend against bacterial infections by ingesting bacteria and releasing antibacterial substances to clear the infection source [113]. In Mycobacterium tuberculosis infection, TNFR1 mediates the innate immune response to help resist the initial infection [114] and by recruiting myeloid cells enhances the host's defense against tuberculosis [110]. The role of TNFR1 in viral infections cannot be ignored. Studies show that TNFR1 promotes the expansion of effector T cells to control viral replication and clear the infection, e.g. the absence of TNFR1 leads to an increase in viral load and worsening of the condition [115–117]. However, the overactivation of TNF-α and TNFR1 may cause tissue damage and even lead to sepsis and other serious consequences, especially in severe coronavirus disease 2019 (COVID-19) cases where the variation of TNFR1 is related to the difference in soluble TNF receptor levels, indicating its immune regulatory role in viral infections [118]. Furthermore, studies have found that blocking TNFR1 significantly improves symptoms and bronchospasm after respiratory syncytial virus (RSV) infection and significantly reduces the levels of various inflammatory cytokines, chemokines, and the number and activation state of neutrophils [119]. TNFR1 also plays an important role in parasitic infection. Studies have shown that TNFR1 is associated with host resistance to infection by certain parasites, such as Toxoplasma gondii, and regulates the host immune response against parasite invasion [120]. A study has shown that TNFR1 loss increases susceptibility to Rickettsia infection, and its pro-inflammatory effects contribute to the expansion of effector T cells [111]. Moreover, mice lacking TNFR1 have a higher survival rate in fatal multiple microbial infections, suggesting a dual role for TNFR1 in regulating immune responses [121].

Cancer

Within the tumor microenvironment, elevated expression of CD147 is correlated with increased tumor aggressiveness and metastasis, whereas TNFR1 is implicated in the regulation of tumor cell apoptosis and the inflammatory response [122–124]. The interaction between CD147 and TNFR1 may influence tumor immune surveillance and facilitate immune evasion. Consequently, TNFR1 not only contributes to tumor progression but also represents a potential therapeutic target, offering novel strategies for cancer treatment. The role of TNFR1 in the tumor microenvironment is multifaceted and critical for understanding tumor biology. TNFR1 not only contributes to tumor initiation and progression but also significantly influences immune cell function within this environment. (1) TNFR1 and tumor growth: T Activation of the TNFR1 signaling pathway limits dendritic cell numbers and function, impairing anti-tumor immunity and facilitating tumor evasion [125]. (2) Dual Role in Cell Survival and Apoptosis: TNFR1 is involved in both apoptosis and survival signaling, allowing tumor cells to survive in adverse conditions while also inducing apoptosis under certain circumstances, making it a potential drug target [126, 127]. (3) Interaction with immune cells: TNFR1 regulates immune cell recruitment, particularly myeloid cells, which often exhibit immunosuppressive properties, aiding tumor evasion [128]. (4) Immunosuppression: TNFR1 activation enhances the immunosuppressive tumor microenvironment by upregulating programmed cell death ligand 1 (PD-L1) on tumor cells, inhibiting T cell activity, and allowing for immune escape [127]. (5) Angiogenesis: TNFR1 also promotes angiogenesis through various signaling pathways, directly stimulating lymphatic endothelial cells and influencing immune cell activity [129, 130].

TNFR1 exhibits different functions in different types of tumors. For example, in gastric cancer, the TNF-α/TNFR1 signaling pathway promotes tumor progression, which may be related to its function in regulating inflammatory responses and cell proliferation [131]. In pancreatic tumors, TNFR1 promotes tumor growth by limiting the function of dendritic cells [125]. TNFR1 is significantly increased in non-small cell lung cancer (NSCLC) cells and is associated with cancer stemness, dedifferentiation, and metastasis [132]. Studies have also found that the expression of TNF is related to the invasiveness and metastasis of breast cancer, and TNFR1 targeted drugs can slow down tumor growth and metastasis by inhibiting the TNF signaling pathway. Combined with immune checkpoint inhibitors, they may enhance antitumor immune responses and improve treatment outcomes [133]. In hematological malignancies, the role of TNFR1 is complex, with its activation potentially inhibiting the growth of certain tumor cells in some cases and promoting proliferation and resistance to treatment in other cases [134]. TNFR1 targeted drugs have shown potential in the treatment of melanoma, as melanoma cells often upregulate PD-L1 to evade immune surveillance, and TNF may weaken the effects of immune checkpoint inhibitors by stabilizing the expression of PD-L1. Using TNFR1 inhibitors can lower the expression of PD-L1 and enhance the effects of immunotherapy [135]. High levels of TNF are associated with poor prognosis in colorectal cancer patients, and TNFR1 targeted therapy has shown potential to improve survival rates in clinical trials by targeting TNFR1 and intervening in the chronic inflammation of the tumor microenvironment to inhibit tumor growth [133].

Metabolic disease

The role of TNFR1 in metabolic diseases, particularly its involvement in metabolic regulation, has garnered significant attention. Its relationship with conditions such as obesity and diabetes are multifaceted.

TNFR1 is pivotal in adipose tissue function and metabolic regulation. Increased levels of TNF-α and TNFR1 are observed in obesity, correlating with inflammation in adipose tissue [136]. Research indicates that TNFR1 knockout models exhibit reduced pro-inflammatory cytokines and improved insulin sensitivity [137, 138]. Moreover, TNFR1 regulates basal metabolic rate and fatty acid oxidation, influencing energy metabolism to mitigate weight gain [139]. In mice lacking TNFR1, enhanced thermogenic mechanisms provide protection against diet-induced obesity [140], suggesting that TNFR1 modulation could be a strategy to address obesity through improved energy balance.

In type 2 diabetes, TNFR1 is linked to inflammation and insulin resistance [141, 142]. Elevated TNFR1 levels impede insulin signaling by inhibiting key signaling pathways, including those involving tyrosine kinases, and activate pro-inflammatory cascades like NF-κB and JNK [143, 144]. In individuals with obesity and type 2 diabetes, the levels of TNF-α and its receptors are commonly elevated, positively correlating with the degree of insulin resistance. This disruption in insulin receptor substrate function exacerbates hyperglycemia. Elevated TNFR1 levels in diabetic individuals correlate with increased insulin resistance and higher mortality risk, highlighting its potential as a therapeutic target [143, 145]. A study showed that Biochemical analysis of blood and urine from diabetic rats (adult-DMA and elderly-DME) and a control group showed reduced TNFR1 expression in various tissues (heart, liver, kidney) in DMA rats, while TNFR1 positively correlated with blood glucose in DME rats. This indicates that early high blood sugar affects inflammation and metabolism-related gene expression, which aging modifies [146].

TNFR1 also plays a significant role in the development of Non-alcoholic fatty liver disease (NAFLD). Patients exhibit increased serum TNF-α and soluble TNFR1 levels, which correlate with disease severity [147]. TNF-α activates inflammatory pathways via TNFR1, contributing to hepatic inflammation, steatosis, and hepatocyte apoptosis, thus exacerbating liver damage [148, 149]. In addition, TNFR1 levels in plasma are associated with Chronic kidney disease (CKD) progression, likely due to renal inflammatory responses affecting kidney function [150]. Targeting TNFR1 may slow disease progression and improve outcomes.

Other diseases

TNFR1 is closely related to a variety of diseases, including central nervous system (CNS) diseases, cardiovascular diseases, and respiratory system diseases.

TNF plays a complex role in the CNS, exhibiting both beneficial and detrimental effects. The expression of TNF and its receptors (TNFR1 and TNFR2) across various cell types significantly influences neural activity and myelin maintenance. Notably, TNFR1 activation is often linked to neuronal apoptosis, especially following ischemic events or other neurological injuries [151, 152]. This dual nature underscores the importance of TNFR1 in neuroinflammation and various neurological disorders, like Alzheimer's disease (AD) [153], multiple sclerosis (MS) [154] and Parkinson's disease (PD) [133]. In AD, TNFR1 interacts with mitochondrial apoptosis-inducing death domain, promoting neuronal death and contributing to characteristic neuronal damage [152]. TNFR1 may also facilitate abnormal amyloid precursor protein processing and β-amyloid plaque formation—key AD pathologies [153]. Furthermore, activation of TNFR1 has also been associated with learning deficits, further emphasizing its potential role in cognitive function decline [153]. Interestingly, while TNFR1 promotes apoptosis, it also exhibits neuroprotective effects, suggesting its potential as a therapeutic target in AD [4]. Inhibition of TNFR1 and preserving TNFR2 signaling integrity has been shown to alleviate neurodegenerative changes [155]. In MS, TNFR1 plays a crucial role in disrupting the blood-brain barrier, allowing inflammatory cells to penetrate the CNS [154]. This dysfunction is associated with demyelination and neuronal apoptosis, contributing to neurological decline [156]. The TNFR1 signaling pathway releases pro-inflammatory cytokines, creating a vicious cycle that exacerbates inflammation and disease progression [157]. While TNFR2 is generally neuroprotective, the pro-inflammatory actions of TNFR1 highlight the need for a balanced receptor response [156]. Targeted therapies using anti-TNFR1 antibodies are being explored to mitigate neurological damage and slow MS progression, with promising results in animal models [158, 159].

TNFR1 plays a critical role in cardiovascular diseases, with studies indicating that elevated TNFR1 levels in acute myocardial infarction (AMI) patients correlate with increased mortality risk, underscoring its role in disease onset and progression [160]. TNF-α and its receptors, including TNFR1, are integral to atherosclerosis development [161, 162]. TNF-α activates endothelial cells, enhancing the recruitment of inflammatory cells, which contribute to arterial wall inflammation and damage, thereby promoting plaque formation and accelerating atherosclerosis progression [163, 164]. Excessive TNFR1 activation also promotes apoptosis in smooth muscle cells, reducing protective cell populations and advancing lesion development [164]. TNFR1 signaling exacerbates atherosclerosis through upregulation of chemokines and adhesion molecules, further attracting inflammatory cells [163, 164]. In low-density lipoprotein receptor (LDLR)-deficient mice, TNFR1 deficiency significantly reduced atherosclerosis, indicating its role in inflammatory mediation and endothelial function [165]. In heart failure, TNF-α and TNFR1 levels are positively correlated with disease severity [166], with TNFR1 activation linked to increased cardiac inflammation, remodeling, and oxidative stress, which exacerbate cardiomyocyte apoptosis and impair cardiac function [167–169]. In ischemic heart disease, TNFR1 expression nearly doubles during cardiac reperfusion injury [170], and a temporal shift in TNF-α expression in CD4 + T lymphocytes suggests TNFR1's involvement in the underlying cardiovascular pathology [168]. However, some studies suggest that inhibiting TNFR1 may not consistently improve outcomes in coronary heart disease or ischemic stroke, indicating a complex role for TNFR1 in these conditions [162].

In chronic obstructive pulmonary disease (COPD), TNFR1 activation is critical, primarily driving chronic airway inflammation and structural damage. Harmful stimuli raise TNF-α levels, which activates TNFR1, triggering immune cell recruitment and sustained inflammatory responses, leading to chronic airway inflammation and damage [171, 172]. TNFR1 also promotes alveolar cell apoptosis, central to emphysema development [172], and contributes to tissue remodeling by stimulating smooth muscle and fibroblast proliferation, worsening airway obstruction [173, 174]. Genetic variations in TNFR1 may affect individual COPD susceptibility [174], with gene polymorphisms linked to varied inflammatory responses. Inhibiting TNF-α or blocking TNFR1 has shown potential in slowing lung function decline and inflammation in COPD models [173]. In asthma, elevated TNF-α levels highlight TNFR1's role in promoting airway inflammation and hyperresponsiveness. TNFR1 activation triggers inflammatory mediator release and remodeling processes that exacerbate airway obstruction [175, 176]. It also induces apoptosis in airway smooth muscle

cells and immune cells in asthma [172, 177]. Asthmatic patients with higher TNFR1 levels generally exhibit more severe symptoms and medication dependence [177, 178]. In pulmonary fibrosis, TNFR1 exerts dual effects, both amplifying inflammation by recruiting inflammatory cells and promoting fibroblast proliferation and collagen deposition, accelerating fibrosis [179, 180]. TNFR1 signaling in pulmonary macrophages further escalates local inflammation [181], and interactions with Fas signaling pathways may exacerbate disease progression [182].

Overall, TNFR1's multifaceted roles across various diseases underscore its significance as a therapeutic target. Continued investigation into TNFR1 signaling mechanisms will be essential for developing effective targeted therapies.

Research progress of targeted TNFR1 therapies

Anti-TNF biologics, while effective in autoimmune diseases, can induce immunosuppression, risking infections [112]. Thus, selective TNFR1 inhibitors are emerging as a research priority to target TNFR1 signaling specifically, potentially reducing systemic side effects and enhancing treatment safety and efficacy [1].

Clinical trials of anti-TNFR1 agents

Despite no TNFR1 targeted drugs yet approved by the market, the current clinical trials show promising prospects, and future research directions will be broader, covering drug development, therapeutic target selection, and clinical application, etc. Five TNFR1 agonists and antagonists registered in clinical trials are listed Table 1.

Antagonist

SAR441566 (Balinatunfib), represents the first small molecule targeting TNFR1 to enter Phase I clinical trials, marks a significant advancement in the treatment of TNFR1-related conditions [183]. Developed by Sanofi, SAR441566 is an oral TNFR1 inhibitor that disrupts the interaction between TNFα and TNFR1 by altering the conformation of soluble TNFα trimers, while preserving the signaling pathways associated with membrane-bound TNFα. Consequently, SAR441566 aims to enhance efficacy and minimize infection risks, offering a convenient oral alternative for chronic autoimmune disease management [183]. In a Phase 1b clinical trial focused on psoriasis treatment, SAR441566 demonstrated promising safety and symptom improvement. Phase II trials for psoriasis and rheumatoid arthritis are ongoing, with results anticipated by 2025.

Table 1 Clinical trials of anti-TNFR1 agents

Therapeutic agents	Description	NCT number	Phases	Conditions	Manufacturer
SAR441566, Balinatunfib	TNFR1 antagonists (Small molecule)	NCT06073093	II	Rheumatoid arthritis	Sanofi
		CTR20241078	II		Aptuit (Verona) Srl
		NCT06073119	II	Plaque psoriasis	Sanofi
		CTR20241003	II		Aptuit (Verona) Srl
		NCT05453942	I	Psoriasis	Sanofi
GSK2862277	TNFR1 antagonists (nano-antibody)	NCT02221037	II [*]	Respiratory Distress Syndrome, Adult	GSK Plc
		EUCTR2014-000643-33-GB	IIa[&]	Acute Lung Injury	
		NCT01818024	I[#]	Respiration disorders	
GSK1995057		NCT01587807	I[#]	Respiration disorders	
Atrosab	TNFR1 antagonists (Monoclonal antibody)	DRKS00004400	I[#]	Inflammatory bowel diseases; Multiple sclerosis; Psoriasis; Rheumatoid arthritis	Baliopharm AG
ATM001, Atrosimab		NCT04650126	I[#]	Chronic liver disease	
VB-111, Ofra-Vec, Ofranergene obadenovec	TNFR1 agonists, FasR agonists (Gene therapy)	NCT03398655	III[#]	Recurrent Platinum-Resistant Ovarian Carcinoma	Vascular Biogenics Ltd.
		NCT02511405	III[#]	Recurrent Glioblastoma	
		NCT01229865	II [#]	Differentiated Thyroid Gland Carcinoma	
		NCT04406272	II [*]	Glioblastoma Multiforme	
		NCT01260506	II [#]		
		NCT00559117	I[#]	Neoplasm Metastasis	
		NCT04166383	II [#]	Colorectal Liver Metastases, Metastatic Colorectal Carcinoma	National Cancer Institute

Note: "[#]" indicates that the clinical trial was Completed, "[*]" indicates that the clinical trial was Terminated, "[&]" indicates that the clinical trial is not yet recruiting, others is ongoing

Novel nano-antibodies, GSK2862277 and GSK1995057, show potential in respiratory distress syndrome and lung injury treatment. In the Phase I trial, GSK2862277 was well tolerated via both inhaled and intravenous administration [184], reduced lung permeability and inflammation biomarkers [185]. However, adverse effects related to binding with human anti-VH autoantibodies highlight challenges in developing biological antagonists for this receptor class [184]. These effects may have contributed to the suspension of Phase II trials. GSK1995057, a single heavy chain variable domain antibody, completed a Phase I trial assessing safety, tolerability, and pharmacokinetics in healthy subjects challenged with inhaled endotoxin. It effectively mitigated pulmonary inflammation and lung injury in macaque models and reduced pulmonary neutrophilia and inflammatory cytokine release in human trials [186], presenting a new option for acute respiratory distress syndrome prevention.

Monoclonal antibodies, Atrosab and Atrosimab (ATM001), exhibit therapeutic effects in preclinical studies by blocking TNFR1 signal transduction, inhibiting tumor proliferation, and enhancing immune cell tumor accumulation [125, 187]. Atrosab has neutralizing activity against TNFR1 and can selectively inhibit the pro-inflammatory activity of TNF while preserving TNFR2-mediated immune regulation and neuroprotection [155]. In animal models, Atrosab has shown potential therapeutic effects in a variety of diseases, including IBD, psoriasis, RA, MS, and acute neurodegenerative diseases [125, 155, 187]. Phase I trials indicated good safety but noted dose-limiting adverse effects, potentially due to the bivalent binding of TNFR1 and its receptor activation [1]. Atrosimab, derived from Atrosab, has completed Phase I trials for chronic liver disease, effectively blocking TNFR1 and lymphotoxin α (LTα) signal, offering potential over traditional anti-TNF drugs in lymphatic system-related conditions [187]. Clinical evidence supports its therapeutic efficacy in inflammatory states and as a safe drug option [187], with significant reductions in inflammatory markers and symptom improvements in multiple sclerosis and acute neurodegenerative diseases [188].

Agonist

VB-111 (Ofra-Vec or Ofranergene obadenovec) a non-integrating, replication-deficient adenovirus type 5 vector, encodes a chimeric death receptor bridging intracellular Fas cell surface death receptor (Fas) to human TNFR1, acting as a dual agonist [189]. VB-111 represents an innovative anti-cancer gene therapy that induces apoptosis and elicits a specific immune response by targeting tumor vascular endothelium [190]. Phase III trials have shown its promise in recurrent platinum-resistant ovarian carcinoma [190] and recurrent glioblastoma [189], underscoring the need for expanded studies to assess its broad applicability in various cancers and inflammatory diseases. Future multi-center trials will be crucial for comprehensive clinical data, enhancing our understanding of these therapies' efficacy and safety [191, 192].

TNFR1 in preclinical studies

Novel selective TNFα, TNFR1, and their complex inhibitors, these drugs have shown good anti-inflammatory properties and have demonstrated potential applications in multiple inflammatory diseases in preclinical studies [13], such as RA, and Crohn's disease [1, 193].

TNFR1 antagonists registered in preclinical studies are all listed Table 2, suggesting that therapies selectively targeting TNFR1 have superior therapeutic potential compared to complete blockade of TNF therapy. Small molecule drugs modulate TNFR1 signaling by targeting specific molecular pathways, offering the advantages of targeting and oral availability. For example, researchers synthesized 16 zafirlukast derivatives and tested their inhibitory effects on TNFR1 signaling [192, 194, 195], finding that three derivatives significantly improved efficacy, with the best derivative reducing NF-κB activity by 2.2 times and IκBα efficiency by 3.3 times, and increasing relative potency by two orders of magnitude [193]. Certain small molecules, like UCB-6876 and UCB5307, can stabilize the asymmetric form of soluble TNF trimer, hindering its signal transduction and inhibits the biological activity of TNF both in vitro and in vivo, providing possibilities for new treatment of arthritis [196]. Peptide-based allosteric inhibitors that target the active region of TNFR1 could provide novel therapeutic strategies for modulating TNFR1 activity in diseases [191].

R1antTNF is a TNFR1-selective antagonistic TNF mutant. Both R1antTNF and its derivatives, including PEG-R1antTNF and scR1antTNF [197, 198], have demonstrated efficacy in inhibiting inflammation, reducing synovial infiltration, and decreasing the number of osteoclasts, thereby indirectly inducing immunosuppression. Notably, this treatment regimen shows superior effectiveness compared to the existing TNF antagonist Etanercept, without triggering reactivation of viral infections. These findings suggest that selective inhibition of the TNF/TNFR1 pathway holds significant therapeutic potential for the treatment of RA [198].

Monoclonal antibody such as Fv13.7-Fc exhibit competitive inhibition of TNF-mediated TNFR1 signaling by enhancing binding to TNFR1, showing significant therapeutic effects in animal models of autoimmune diseases [199]. In addition, aptamers such as Apt1-67 and Apt2-55nt have been developed to specifically inhibit TNFR1 through separable microneedle delivery systems, indicating it may have the potential to treat RA [200, 201]. Compared to traditional biologics, TNFR1-selective aptamers

Table 2 Relevant studies of preclinical TNFR1 antagonists

Therapeutic agents	Type	Clinical indication	Research results	References
R1antTNF, PEG-R1antTNF, scR1antTNF	Recombinant protein	Induction of Lethal Hepatitis or Collagen Induced Arthritis — mice model	R1antTNF did not activate TNFR1, inhibits NF-κB, decreasing inflammation.	[197, 198]
P60 PLAD		Mouse model of systemic lupus erythematosus	NF-κB, monocyte chemotactic protein 1, and inducible nitric oxide synthase expression in skin lesions were significantly inhibited.	[209]
C7 or SGT11	Allosteric modulator	Traumatic brain injury	Decreased cortical inflammatory cytokines	[210]
Fv13.7-Fc	Monoclonal antibody	Mouse model of Autoimmune diseases	Exhibited increased binding to TNFR1 and superior inhibition of TNF-mediated TNFR1 activation, while lacking any agonistic activity even in the presence of cross-linking antibodies.	[199]
IZI-06.1		Rheumatoid arthritis	TNFR1 antibodies, specifically bound to the cysteine-rich domain 1 of TNFR1 with high affinity and complete blockage.	[192, 211]
OBI-TNF-α^{WT}, OBI-TNF-α^{MUT}		B cell non-Hodgkin's Lymphoma	CD20/TNFR1 dual-targeting antibody enhances lysosome rupture-mediated cell death in B cell lymphoma	[207]
TNFR1-AlbudAb		Human rheumatoid arthritis synovial membrane mononuclear cells	Mediated cell apoptosis in Kym-1 cells and decreased the expression of IL-1β, GM-CSF, IL-6, IL-8, MCP-1 and RANTES in mononuclear cells	[192, 212]
Apt1-67, apt2-55nt	Aptamer	Mouse model of rheumatoid arthritis	Aptamer, which specifically inhibits TNF receptor 1 via separable microneedles.	[200, 201]
UCB-6876, UCB5307	Small molecule	Mouse model of arthritis	Stabilise an asymmetrical form of the soluble TNF trimer, compromising signalling and inhibiting the functions of TNF in vitro and in vivo.	[196]
DS41, DSA11, Zafirlukast		IκBα degradation and NF-κB activation assays in HEK293 cells	Inactivate pro-inflammatory NF-κB signaling.	[192, 194]
R7050, Zafirlukast (Zaf)		Trichloroethylene sensitized mice model	R7050 can relieve M1 macrophage autophagy. Zaf reduce CD11c and TNFR1, and decrease p-mTOR expression.	[195]

also contribute to reduce treatment costs for patients while minimizing adverse effects. In such, the development of TNFR1-targeted drugs provides new options for the treatment of various inflammatory diseases and cancers.

In addition to the development of inhibitors targeting TNFR1, researchers are increasingly investigating TNFR1 agonists. The exploration of TNFR1 agonists not only advances our understanding of disease pathogenesis but also uncovers unique therapeutic potentials for specific conditions. R32W-S86T, a TNFR1-selective TNF mutant protein, has been identified as capable of activating TNFR1 [202]. Experimental results demonstrate that R32W-S86T significantly enhances the translocation of 125I-labeled albumin across HUVEC monolayers, indicating that R32W-S86T stimulation of TNFR1 increases the permeability of these endothelial cell layers. Concurrently, R32W-S86T induces substantial actin cytoskeletal reorganization, which is accompanied by cellular retraction and the formation of intercellular gaps, thereby contributing to the observed increase in permeability. The augmented vascular permeability mediated by TNFR1 activation may elucidate the pathophysiological effects of TNF during acute inflammatory responses, such as those observed in septic shock, systemic inflammatory response syndrome, or acute respiratory distress syndrome (ARDS).

hTNF/CHP is a human TNF/CHP nanogel complex that activates TNFR1 [203]. Micro-computed tomography (micro-CT) reconstruction images demonstrate that hTNF/CHP significantly induces bone resorption lacunae in mouse calvariae, a pathological hallmark of chronic inflammatory diseases such as rheumatoid arthritis and periodontitis [204]. Brain metastasis presents a significant clinical challenge, with the blood-brain barrier (BBB) serving as a critical obstacle to effective systemic therapy [205]. Enhancing the permeability of the BBB facilitates improved drug delivery to the CNS, which is crucial for the treatment of brain cancer, as conventional chemotherapy agents often struggle to penetrate the BBB. G4-mutTNF, a TNFR1-selective agonist variant of human TNF, has been identified as capable of selectively increasing BBB permeability, thereby enhancing the delivery efficiency of therapeutic agents to brain metastases [206]. The selective action of G4-mutTNF offers the potential to minimize non-specific systemic side effects while preserving the integrity of the cerebrovascular system.

While the exploration of TNFR1 agonists has demonstrated their research value by providing insights into disease mechanisms and highlighting distinct therapeutic potential in specific conditions, researchers may also be weighing the potential risks associated with these agents. For instance, TNFR1 agonists can elevate the risk of infection and inflammation, which may deter researchers

from initiating studies involving them due to concerns about unpredictable outcomes.

Combined therapy with TNFR1 inhibitor

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly inflammatory microenvironment with a paucity of dendritic cells (DCs), a condition linked to the tumor's aggressive nature. The study demonstrated that the inhibition of TNFR1, either through gene ablation or antibody intervention, enhances T cell activation within the tumor milieu and decelerates PDAC progression [125]. Monotherapy with anti-PD-1 checkpoint inhibitors exhibits limited efficacy against PDAC; however, when combined with anti-TNFR1 agents, there is a notable augmentation in T cell activation, thereby improving therapeutic outcomes. The blockade of TNFR1 signaling via anti-TNFR1 antibodies potentially mitigates the detrimental impact on DCs, facilitating enhanced T cell activation. Concurrently, the inhibition of the PD-1/PD-L1 axis by PD-1 antibodies can counteract tumor-induced immune evasion, thereby bolstering T cell-mediated antitumor activity. This combinatorial treatment approach significantly diminishes the presence of F4/80 + and CD206 + macrophages, which are typically associated with immunosuppressive functions within the tumor microenvironment. Meanwhile, the combination treatment demonstrated a significant increase in CD8 + T cells and upregulation of granzyme B expression, indicative of an enhanced cytotoxic response against tumor cells. This therapeutic approach underscores the potential of targeting the tumor microenvironment to treat cancers driven by oncogenes and to overcome the resistance associated with targeted therapies.

Obinutuzumab, an antibody utilized in the treatment of B-cell non-Hodgkin lymphoma (BNHL), and TNFR1-induced cell death both operate through lysosome membrane permeabilization (LMP). The combination of TNFR1 and Obinutuzumab, formulated as the Obinutuzumab-TNF-α fusion protein (OBI-TNF-α^{MUT}), serves as a CD20/TNFR1 dual-targeting antibody. This innovative approach enhances LMP-mediated cell death and further augmented antibody-dependent cellular cytotoxicity (ADCC) [207]. OBI-TNF-α^{MUT} is capable of inhibiting NF-κB activation in the presence of TNF-α, indicating its potential to counteract the proliferative effects of TNF-α in cancer. Consequently, OBI-TNF-α^{MUT} may offer a precision therapeutic option for patients with BNHL, particularly those exhibiting upregulated TNFR1 expression.

The researchers induced experimental autoimmune encephalomyelitis (EAE) in humanized *Tnfr1*$^{-/-}$ mice through the administration of a human-specific TNFR1 selective antagonist (H398) and a murine-specific TNFR2 agonist (EHD2-sc-mTNFR2), both individually and in combination [208]. The modulation of TNFR pathways effectively ameliorated EAE symptoms and led to a reduction in demyelination, inflammatory infiltration, and axonal degeneration. Furthermore, the combined therapeutic approach of inhibiting TNFR1 and activating TNFR2 signaling enhanced the survival of retinal ganglion cells (RGCs) and facilitated the phosphorylation of Akt and NF-κB. These findings suggest that the concurrent modulation of TNFR1 and TNFR2 activity may offer novel therapeutic strategies for the treatment of inflammatory demyelinating diseases, such as multiple sclerosis.

Conclusion and prospect

TNFR1 is a pivotal cell surface receptor that activates intracellular signaling networks through its interaction with TNF-α. The activation of TNFR1 initiates multiple signaling pathways, such as NF-κB, MAPK pathways, which play critical roles in regulating cellular growth, apoptosis, immune responses, and inflammatory processes. Given its integral role in these biological mechanisms, TNFR1 has emerged as a prominent target in the field of drug development. By precisely modulating the TNFR1 signaling pathway, it is possible to devise innovative therapeutic strategies aimed at addressing a spectrum of diseases associated with dysregulated TNFR1 signaling, including but not limited to inflammatory disorders, cancers, metabolic syndromes, and infectious diseases.

Recent advancements in research suggest that scientists are actively engaged in developing strategies for the selective targeting of TNFRs. This involves the use of TNFR1 antagonists in conjunction with TNFR2 agonists to preserve the protective signaling mediated by TNFR2 while mitigating the detrimental effects associated with TNFR1-mediated signaling. This approach is designed to mitigate the pro-inflammatory effects associated with TNFR1 activation while preserving the immunoregulatory functions of TNFR2, thereby providing novel therapeutic avenues for related pathologies. Although no targeted therapies for TNFR1 are currently available on the market, ongoing clinical trials and preclinical studies are evaluating the efficacy and safety of novel TNFR1 inhibitors, bolstered by a deeper comprehension of TNFR1 and its signaling mechanisms.

Future research is essential to elucidate the functional mechanisms of the TNFR1 signaling pathway across various disease states. Targeted interventions on TNFR1 and downstream components are vital for drug discovery. Comprehensive research may uncover biomarkers and targets, enabling precise clinical strategies. As insights into TNFR1 mechanisms grow, new pharmacological agents and therapies, including monotherapy and combinations with immune checkpoint

inhibitors, are anticipated. Genomic profiling could personalize TNFR1-targeted treatments. Research should also explore novel administration routes, such as oral, localized, and biovector systems, to enhance bioavailability and specificity, potentially improving patient compliance and reducing side effects. Selective TNFR1 targeting promises improved efficacy and safety over traditional anti-TNF therapies, offering hope for patients [192].

In conclusion, the TNFR1 signaling pathway plays a crucial role in the regulation of cellular states, modulation of inflammatory responses, and the progression of cancer. As research on TNFR1 signaling continues to evolve, it offers a promising avenue for the identification of novel therapeutic targets or to develop new treatment strategies, and enhances our comprehension of the underlying mechanisms of various complex diseases. This advancement will contribute to the development of personalized medicine and precision therapeutics, representing a significant advancement in the treatment of numerous diseases associated with dysregulation of TNFR1 signaling.

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